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(54) Title: NOVEL 2-AMINO-4-OXOQUINAZOLONES AS LXR NUCLEAR RECEPTOR BINDING COMPOUNDS WITH PARTIAL AGONISTIC PROPERITES

(I)
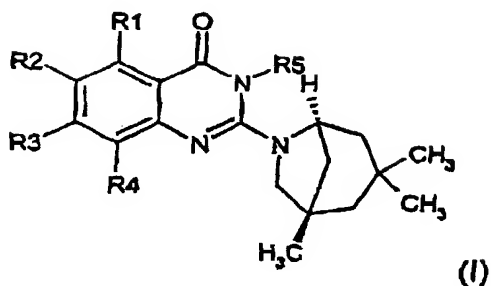
(57) Abstract: The present invention relates to compounds according to the general formula (I) which bind to the Liver X receptors (LXR receptors, LXRalpha/NR1H3 and LXRbeta/NR1H2) and act as selective agonists of the LXR receptors. The invention further relates to the treatment of diseases and/or conditions through binding of said nuclear receptors and selective agonistic effects by said compounds and the production of medicaments using said compounds. In particular the compounds are useful in the treatment of hypercholesterolemia, obesity or other diseases associated with elevated lipoprotein (LDL) levels.

NOVEL 2-AMINO-4-OXOQUINAZOLONES AS LXR NUCLEAR RECEPTOR BINDING COMPOUNDS WITH PARTIAL AGONISTIC PROPERTIES

Liver X Receptor (LXR) is a prototypical type 2 nuclear receptor which activates
10   genes upon binding to promoter region of target genes in a prototypical heterodimeric
fashion with Retinoid X Receptor (hereinafter RXR, Forman et al., Cell, 81, 687-93,
1995). The term LXR includes all subtypes of this receptor. Specifically LXR includes
LXRa (also known as LXRalpha, RLD-1 and NR1H3) and LXRb (also known as
LXRbeta, NER, NER1, UR, OR-1, R1P15 and NH1H2) and ligands of LXR should be
15   understood to include ligands of LXRa or LXRb. The relevant physiological ligands
of LXR seem to be oxidized derivatives of cholesterol, including 22-
hydroxycholesterol and 24,25(S)-epoxycholesterol (Lehmann, et al., Biol. Chem.
272(6), 3137-40, 1997). The oxysterol ligands bound to LXR were found to regulate
the expression of several genes that participate in cholesterol metabolism (Janowski,
20   et al., Nature, 383, 728-31, 1996).

LXR is proposed to be a hepatic oxysterol sensor. Upon activation (e.g. binding of
oxysterols) it influences the conversion of dietary cholesterol into bile acids by
upregulating the transcription of key genes which are involved in bile acid synthesis
25   such as CYP7A1. Hence, activation of LXR in the liver could result in an increased
synthesis of bile acids from cholesterol which could lead to decreased levels of
hepatic cholesterol. This proposed LXR function in hepatic cholesterol metabolism
was experimentally confirmed using knockout mice. Mice lacking the receptor LXRa
lost their ability to respond normally to an increase in dietary cholesterol and did not
30   induce transcription of the gene encoding CYP7A1. This resulted in accumulation of
large quantities of cholesterol in the livers and impaired hepatic function (Peet, et al.,
Cell, 93, 693-704, 1998).

Besides its important function in liver, LXR plays an important role in the regulation of
35   cholesterol homeostasis in macrophages and intestinal mucosa cells where it
upregulates cholesterol transporters from the ABC (=ATP binding cassette) family of
membrane proteins (Repa, et al., J Biol Chem. 2002 May 24;277(21):18793-800).

5   These transporters are believed to be crucially involved in the uptake of cholesterol
     from the diet since mutations in their genes leads to diseases such as sitosterolemia
     (Berge, et al., Science (2000);290(5497):1771-5.).

     Other members of the ABC transporter family seem to be responsible for the efflux of
10   cholesterol from loaded macrophages, a process which is thought to prevent the
     generation of atherosclerotic lesions. Stimulation of LXR by synthetic ligands might
     result in an increased cholesterol efflux from macrophages and a decreased building
     up of cholesterol loaded atherosclerotic plaques (Venkateswaran, et al., PNAS
     (2000) 24;97(22):12097-102; Sparrow, et al., J Biol Chem (2002) 277(12):10021-7;
15   Joseph, et al., PNAS (2002);99(11):7604-9). Direct evidence that synthetic LXR
     ligands inhibit the development of atherosclerosis has been provided in two animal
     models of atherosclerosis: A significant reduction in the formation of atherosclerotic
     plaques were shown in two studies in animal models using full LXR agonists Joseph
     et al. PNAS (2002) 99:7604-9 and Terasaka et al. (2003) Terasaka et al. FEBS Lett.
20   (2003) 536:6-11. In addition, two recent reports have highlighted the potential use of
     LXR agonists in diabetes (Cao et al., (2003) J Biol Chem. 278:1131-6 and
     inflammatory disorders (Joseph et al., (2003) Nat Med. 9:213-9.

     However, in animal studies it was observed that activation of LXR in the liver by full
25   agonists like T0901317 does not only increase bile acid synthesis but also stimulates
     the de novo synthesis of fatty acids and triglycerids through the upregulation of key
     enzymes such as Fatty Acid Synthase (FAS) or Stearyl-CoA Desaturase (SCD-1)
     (Schultz, et al., Genes Dev (2000) 14(22):2831-8). Elevation of serum triglyceride
     levels is an indendent risk factor for atherosclerosis (for review see Miller (1999)
30   Hosp Pract (Off Ed) 34: 67-73.).

     Thus, LXR activity needs to be selectively modulated for therapeutic benefit. In
     particular, compounds need to be found that stimulate reverse cholesterol transport,
     but do not significantly increase trigclyceride levels. This might be particular relevant
35   for the usage of such compounds in diabetic patients since a even more severe
     lopogenic effect was reported for the full agonist T0901317 in db/db mice which serve
     as an animal model for diabetes (Chisholm et al. (2003) J.Lipid Res (epub August
     16)).

5

Therefore, an ideal synthetic LXR binding compound should have properties that retain the agonistic activity on hepatic bile acid formation and ABC-transporter - mediated decrease in cholesterol uptake from the diet and increased cholesterol efflux from macrophages. In parallel such a compound should lack the hyperlipidemic

10   potential which is exerted through increased fatty acid and triclyceride synthesis.

To date only few compounds have been described which bind the LXR receptor and thus show utility for treating diseases or conditions which are due to or influenced by said nuclear receptor (Collins, et al., J Med Chem. (2002) 45(10):1963-6; Schultz, et

15   al., Genes Dev (2000) 14(22):2831-8; Sparrow, et al., J Biol Chem (2002) 277(12):10021-7). No non-steroidal compounds have so far been described which show selectivity regarding the induction of ABC transporter genes without simultaneous induction of lipogenic genes like FAS and SREBP-1c (Kaneko et al. (2003) J Biol Chem (epub July 7).

20

It is thus an object of the invention to provide for compounds which by means of binding the LXR receptor act as partial agonists of said receptor with a selective property regarding the upregulation of genes like the ABC transporters in macrophages and/or other cell types and a stronlgy reduced liability to increase the

25   expression of genes involved in triglyceride synthetic pathways (like FAS and SREBP-1c). These compounds should show utility for treating diseases or conditions which are due to or influenced by said nuclear receptor.

It is further an object of the invention to provide for compounds that may be used for

30   the manufacture of a medicament for the treatment of cholesterol associated conditions or diseases. It is still a further object of the invention to provide for compounds that lower serum cholesterol and/or increase High Density Lipoproteins (HDL) and/or decrease Low Density Lipoproteins (LDL). It is also an object of the invention to provide for compounds that may be used for the treatment of lipid

35   disorders including hypercholesterolemia, atherosclerosis, Alzheimer's disease, skin disorders, inflammation, obesity and diabetes.

5   The present invention provides, *inter alia*, novel LXR nuclear receptor protein binding
     compounds according to the general formula (I) shown below. Said compounds are
     also binders of mammalian homologues of said receptor. Further the object of the
     invention was solved by providing for amongst the LXR nuclear receptor protein
     binding compounds according to the general formula (I) such compounds which act

10   as partial agonists or mixed agonists / antagonists of the human LXR receptor or a
     mammalian homologue thereof. Further the object of the invention was solved by
     providing for amongst the LXR receptor protein binding compounds according to the
     general formula (I) such compounds which act as partial agonists of the human LXR
     receptor resulting therefore in the induction of ABC transporter proteins such as

15   ABCA1 or ABCG1 in cell types such as macrophages but lacking a strong potential
     to induce genes involved in triglyceride synthetic pathways such as fatty acid
     synthase (FAS) or SREBP1c.

     The invention provides for LXR agonists that may be used for the manufacture of a
20   medicament for the treatment of cholesterol associated conditions or diseases. In a
     preferred embodiment compounds are provided that lower serum cholesterol and/or
     increase High Density lipoproteins (HDL) and/or decrease Low Density Lipoproteins
     (LDL). Also compounds are provided that may be used for the treatment of lipid
     disorders including hypercholesterolemia, atherosclerosis, Alzheimer´s disease, skin
25   disorders, inflammation, obesity and diabetes.

     The invention provides for a compound of the formula (I), or pharmaceutical
     acceptable salts or solvates thereof, hereinafter also referred to as the "compounds
     according to the invention" including particular and preferred embodiments thereof.
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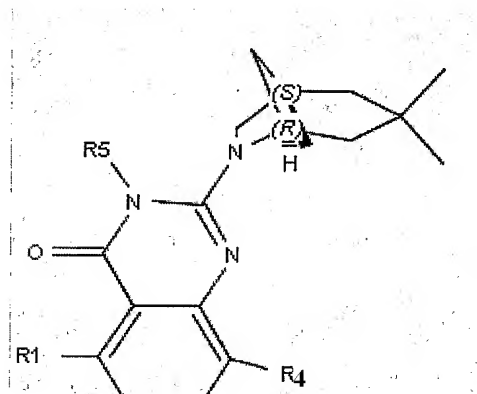
5   (I)

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The compounds of the invention can also exist as solvates and hydrates. Thus, these compounds may crystallize with, for example, waters of hydration, or one, a number

10   of, or any fraction thereof of molecules of the mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

In one embodiment of the invention in formula (I) above, R_1, R_2, R_3, R_4, - independent from each other - H, halogen, hydroxy, protected hydroxy, cyano, nitro,

15   C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6

20   alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or phenyl,

and R_5 is H, C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_7 to C_{12} alkylphenyl or C_7 to

25   C_{12} substituted phenylalkyl.

In an other embodiment of the invention in formula (I) above R_1, R_3 and R_4 are H, R_2 is halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7

30   substituted acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6

35   alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or phenyl,

and R_5 is H, C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl.

5

The symbol "H" denotes a hydrogen atom.

The term "C_1 to C_7 acyl" encompasses groups such as formyl, acetyl, propionyl, butyryl, pentanoyl, pivaloyl, hexanoyl, heptanoyl, benzoyl and the like. Preferred acyl
10   groups are acetyl and benzoyl.

The term "C_1 to C_7 substituted acyl" denotes the acyl group substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo, cyclohexyl, naphthyl, amino, protected amino, (monosubstituted)amino,
15   protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, nitro, C_1 to C_6 alkyl ester, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N,N-di(C_1 to C_6 alkyl)carboxamide, cyano,
20   methylsulfonylamino, thiol, C_1 to C_4 alkylthio or C_1 to C_4 alkylsulfonyl groups. The substituted acyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

The term "substituted phenyl" specifies a phenyl group substituted with one or more,
25   and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino,
30   (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N- (phenylsulfonyl)amino or phenyl, wherein the phenyl is substituted or unsubstituted, such that, for example, a biphenyl results.
35

Examples of the term "substituted phenyl" includes a mono- or di(halo)phenyl group such as 2, 3 or 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2, 3 or 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl,

5   2, 3 or 4-fluorophenyl and the like; a mono or di(hydroxy)phenyl group such as 2, 3 or
     4-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and
     the like; a nitrophenyl group such as 2, 3 or 4-nitrophenyl; a cyanophenyl group, for
     example, 2, 3 or 4-cyanophenyl; a mono- or di(alkyl)phenyl group such as 2, 3 or 4-
     methylphenyl, 2,4-dimethylphenyl, 2, 3 or 4-(iso-propyl)phenyl, 2, 3 or 4-ethylphenyl,
10   2, 3 or 4-(n-propyl)phenyl and the like; a mono or di(alkoxyl)phenyl group, for
     example, 2,6-dimethoxyphenyl, 2, 3 or 4-methoxyphenyl, 2, 3 or 4-ethoxyphenyl, 2, 3
     or 4-(isopropoxy)phenyl, 2, 3 or 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and
     the like; 2, 3 or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected
     carboxy)phenyl group such as 2, 3 or 4-carboxyphenyl or 2,4-di(protected
15   carboxy)phenyl; a mono-or di(hydroxymethyl)phenyl or (protected
     hydroxymethyl)phenyl such as 2, 3, or 4-(protected hydroxymethyl)phenyl or
     3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected
     aminomethyl)phenyl such as 2, 3 or 4-(aminomethyl)phenyl or 2,4-(protected
     aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 2, 3
20   or 4-(N-(methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents
     disubstituted phenyl groups wherein the substituents are different, for example, 3-
     methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl,
     4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy 4-chlorophenyl and the
     like.

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     The term "heteroaryl" means a heterocyclic aromatic derivative which is a five-
     membered or six-membered ring system having from 1 to 4 heteroatoms, such as
     oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction
     with sulfur or oxygen ring atoms. Examples of heteroaryls include pyridinyl,
30   pyrimidinyl, and pyrazinyl, pyridazinyl, pyrrolo, furano, thiopheno, oxazolo, isoxazolo,
     phthalimido, thiazolo and the like.

     The term "substituted heteroaryl" means the above-described heteroaryl is
     substituted with, for example, one or more, and preferably one or two, substituents
35   which are the same or different which substituents can be halogen, hydroxy,
     protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted
     alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, protected
     carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected

5   hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected
(monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide,
N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1
to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino or N-
(phenylsulfonyl)amino groups.

10

The term "substituted naphthyl" specifies a naphthyl group substituted with one or
more, and preferably one or two, moieties either on the same ring or on different
rings chosen from the groups consisting of halogen, hydroxy, protected hydroxy,
cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy,

15   protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl,
protected hydroxymethyl, amino, protected amino, (monosubstituted)amino,
protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected
carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6
alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6

20   alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino.

Examples of the term "substituted naphthyl" includes a mono or di(halo)naphthyl
group such as 1, 2, 3, 4, 5, 6, 7 or 8-chloronaphthyl, 2, 6-dichloronaphthyl, 2, 5-
dichloronaphthyl, 3, 4-dichloronaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-bromonaphthyl, 3, 4-

25   dibromonaphthyl, 3-chloro-4-fluoronaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-fluoronaphthyl and
the like; a mono or di(hydroxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-
hydroxynaphthyl, 2, 4-dihydroxynaphthyl, the protected-hydroxy derivatives thereof
and the like; a nitronaphthyl group such as 3- or 4-nitronaphthyl; a cyanonaphthyl
group, for example, 1, 2, 3, 4, 5, 6, 7 or 8-cyanonaphthyl; a mono- or

30   di(alkyl)naphthyl group such as 2, 3, 4, 5, 6, 7 or 8-methylnaphthyl, l, 2,
4-dimethylnaphthyl, l, 2, 3, 4, 5, 6, 7 or 8-(isopropyl)naphthyl, l, 2, 3, 4, 5, 6, 7 or
8-ethylnaphthyl, l, 2, 3, 4, 5, 6, 7 or 8-(n-propyl)naphthyl and the like; a mono or
di(alkoxy)naphthyl group, for example, 2, 6-dimethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or
8-methoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-ethoxynaphthyl, l, 2, 3, 4, 5, 6, 7 or

35   8-(isopropoxy)naphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(t-butoxy)naphthyl, 3-ethoxy-4-
methoxynaphthyl and the like; 1, 2, 3, 4, 5, 6, 7 or 8-trifluoromethylnaphthyl; a mono-
or dicarboxynaphthyl or (protected carboxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7
or 8-carboxynaphthyl or 2, 4-di(-protected carboxy)naphthyl; a mono-or

5   di(hydroxymethyl)naphthyl or (protected hydroxymethyl)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(protected hydroxymethyl)naphthyl or 3, 4-di(hydroxymethyl)naphthyl; a mono- or di(amino)naphthyl or (protected amino)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(amino)naphthyl or 2, 4-(protected amino)-naphthyl, a mono- or di(aminomethyl)naphthyl or (protected aminomethyl)naphthyl such as 2, 3, or

10   4-(aminomethyl)naphthyl or 2, 4-(protected aminomethyl)-naphthyl; or a mono- or di-(N-methylsulfonylamino) naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(N-methylsulfonylamino)naphthyl. Also, the term "substituted naphthyl" represents disubstituted naphthyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxynaphth-1-yl, 3-chloro-4-hydroxynaphth-2-yl, 2-methoxy-4-

15   bromonaphth-1-yl, 4-ethyl-2-hydroxynaphth-1-yl, 3-hydroxy-4-nitronaphth-2-yl, 2-hydroxy-4-chloronaphth-1-yl, 2-methoxy-7-bromonaphth-1-yl, 4-ethyl-5-hydroxynaphth-2-yl, 3-hydroxy-8-nitronaphth-2-yl, 2-hydroxy-5-chloronaphth-1-yl and the like.

20   The term "C_1 to C_8 alkyl" denotes such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, amyl, tert-amyl, hexyl , n-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 2-methyl-1hexyl, 2-methyl-2hexyl, 2-methyl-3-hexyl, n-octyl and the like.

25   The term "C_2 to C_6 alkenyl" denotes such radicals as propenyl or butenyl.

Examples of the above substituted alkyl groups include the 2-oxo-prop-1-yl, 3-oxo-but-1-yl, cyanomethyl, nitromethyl, chloromethyl, hydroxymethyl, tetrahydropyranyloxymethyl, trityloxymethyl, propionyloxymethyl, amino,

30   methylamino, aminomethyl, dimethylamino, carboxymethyl, allyloxycarbonylmethyl, allyloxycarbonylaminomethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl, trifluoromethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-aminopropyl, 1-chloroethyl, 2-chloroethyl, 1-bromoethyl, 2-chloroethyl, 1-fluoroethyl, 2-fluoroethyl, 1- iodoethyl, 2-iodoethyl, 1-

35   chloropropyl, 2-chloropropyl, 3- chloropropyl, 1-bromopropyl, 2-bromopropyl, 3-bromopropyl, 1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 1- iodopropyl, 2-iodopropyl, 3-iodopropyl, 2-aminoethyl, 1- aminoethyl, N-benzoyl-2-aminoethyl, N-acetyl-2-aminoethyl, N-benzoyl-1-aminoethyl, N-acetyl-1-aminoethyl and the like.

5

The term "C_1 to C_8 substituted alkyl" denotes that the above C_1 to C_8 alkyl groups are substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo, C_3 to C_7 cycloalkyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino,

10 guanidino, protected guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N,N-di(C_1 to C_6 alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C_1 to C_4 alkylthio or C_1 to C_4

15 alkylsulfonyl groups. The substituted alkyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

The term "C_7 to C_{12} phenylalkyl" denotes a C_1 to C_6 alkyl group substituted at any position by a phenyl, substituted phenyl, heteroaryl or substituted heteroaryl.

20 Examples of such a group include benzyl, 2-phenylethyl, 3-phenyl(n-propyl), 4-phenylhexyl, 3-phenyl(n-amyl), 3-phenyl(sec-butyl) and the like. Preferred C_7 to C_{12} phenylalkyl groups are the benzyl and the phenylethyl groups.

The term "C_7 to C_{12} substituted phenylalkyl" denotes a C_7 to C_{12} phenylalkyl group substituted on the C_1 to C_6 alkyl portion with one or more, and preferably one or two,

25 groups chosen from halogen, hydroxy, protected hydroxy, oxo, protected oxo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, protected guanidino, heterocyclic ring, substituted heterocyclic ring, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, nitro,

30 carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-(C_1 to C_6 dialkyl)carboxamide, cyano, N-(C_1 to C_6 alkylsulfonyl)amino, thiol, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfonyl groups; and/or the phenyl group may be substituted with one or more, and preferably one or two, substituents chosen from halogen, hydroxy,

35 protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino,

5   (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino,
carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl) carboxamide, protected N-
(C_1 to C_6 alkyl) carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-
((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino, cyclic C_2 to C_7 alkylene or a
phenyl group, substituted or unsubstituted, for a resulting biphenyl group. The

10   substituted alkyl or phenyl groups may be substituted with one or more, and
preferably one or two, substituents which can be the same or different.

Examples of the term "C_7 to C_{12} substituted phenylalkyl" include groups such as 2-
phenyl-1-chloroethyl, 2-(4-methoxyphenyl)ethyl, 4-(2,6-dihydroxy phenyl)n-hexyl, 2-

15   (5-cyano-3-methoxyphenyl)n-pentyl, 3-(2,6-dimethylphenyl)n-propyl, 4-chloro-3-
aminobenzyl, 6-(4-methoxyphenyl)-3-carboxy(n-hexyl), 5-(4-aminomethylphenyl)- 3-
(aminomethyl)n-pentyl, 5-phenyl-3-oxo-n-pent-1-yl and the like.

20

The term "heterocycle" or "heterocyclic ring" denotes optionally substituted five-
membered to eight-membered rings that have 1 to 4 heteroatoms, such as oxygen,
sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur

25   or oxygen ring atoms. These five-membered to eight-membered rings may be
saturated, fully unsaturated or partially unsaturated, with fully saturated rings being
preferred. Preferred heterocyclic rings include morpholino, piperidinyl, piperazinyl,
2-amino-imidazoyl, tetrahydrofurano, pyrrolo, tetrahydrothiophen-yl,
hexylmethyleneimino and heptylmethyleneimino.

30

The term "substituted heterocycle" or "substituted heterocyclic ring" means the
above-described heterocyclic ring is substituted with, for example, one or more, and
preferably one or two, substituents which are the same or different which substituents
can be halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12}

35   alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, carboxy,
protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl,
protected hydroxymethyl, amino, protected amino, (monosubstituted)amino,
protected (monosubstituted)amino, (disubstituted)amino carboxamide, protected

5   carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12}
     alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12}
     alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino, heterocycle or substituted heterocycle
     groups.

10

     The term "C_1 to C_8 alkoxy" as used herein denotes groups such as methoxy, ethoxy,
     n-propoxy, isopropoxy, n-butoxy, t-butoxy and like groups. A preferred alkoxy is
     methoxy. The term "C_1 to C_8 substituted alkoxy" means the alkyl portion of the alkoxy
     can be substituted in the same manner as in relation to C_1 to C_8 substituted alkyl.

15

     The term "C_1 to C_8 aminoacyl" encompasses groups such as formyl, acetyl,
     propionyl, butyryl, pentanoyl, pivaloyl, hexanoyl, heptanoyl, octanoyl, benzoyl and the
     like.

20   The term "C_1 to C_8 substituted aminoacyl" denotes the acyl group substituted by one
     or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo,
     protected oxo, cyclohexyl, naphthyl, amino, protected amino,
     (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino,
     guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl,
25   pyrrolidinyl, C_1 to C_{12} alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, nitro, C_1 to C_{12} alkyl
     ester, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide,
     N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N,N-di(C_1
     to C_{12} alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C_1 to C_{10} alkylthio or C_1
     to C_{10} alkylsulfonyl groups. The substituted acyl groups may be substituted once or
30   more, and preferably once or twice, with the same or with different substituents.

     Examples of C_1 to C_8 substituted acyl groups include 4-phenylbutyroyl, 3-
     phenylbutyroyl, 3-phenylpropanoyl, 2- cyclohexanylacetyl, cyclohexanecarbonyl, 2-
     furanoyl and 3-dimethylaminobenzoyl.

35

     This invention also provides a pharmaceutical composition comprising an effective
     amount of a compound according to the invention. Such pharmaceutical
     compositions can be administered by various routes, for example oral,

5   subcutaneous, intramuscular, intravenous or intracerebral. The preferred route of
     administration would be oral at daily doses of the compound for adult human
     treatment of about 0.01-5000 mg, preferably 1-1500 mg per day. The appropriate
     dose may be administered in a single dose or as divided doses presented at
     appropriate intervals for example as two, three four or more subdoses per day.

10

     For preparing pharmaceutical compositions containing compounds of the invention,
     inert, pharmaceutically acceptable carriers are used. The pharmaceutical carrier can
     be either solid or liquid. Solid form preparations include, for example, powders,
     tablets, dispersible granules, capsules, cachets, and suppositories.

15

     A solid carrier can be one or more substances which can also act as diluents,
     flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet
     disintegrating agents; it can also be an encapsulating material.

20   In powders, the carrier is generally a finely divided solid which is in a mixture with the
     finely divided active component. In tablets, the active compound is mixed with the
     carrier having the necessary binding properties in suitable proportions and
     compacted in the shape and size desired.

25   For preparing pharmaceutical composition in the form of suppositories, a low-melting
     wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the
     active ingredient is dispersed therein by, for example, stirring. The molten
     homogeneous mixture is then poured into convenient-sized molds and allowed to
     cool and solidify.

30

     Powders and tablets preferably contain between about 5% to about 70% by weight of
     the active ingredient, preferably comprising (especially consisting of) one or more of
     the compounds according to this invention. Suitable carriers include, for example,
     magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin,
35   starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting
     wax, cocoa butter and the like.

5   The pharmaceutical compositions can include the formulation of the active compound
       with encapsulating material as a carrier providing a capsule in which the active
       component (with or without other carriers) is surrounded by a carrier, which is thus in
       association with it. In a similar manner, cachets are also included. Tablets, powders,
       cachets, and capsules can be used as solid dosage forms suitable for oral
10   administration.

       Liquid pharmaceutical compositions include, for example, solutions suitable for oral
       or parenteral administration, or suspensions, and emulsions suitable for oral
       administration. Sterile water solutions of the active component or sterile solutions of
15   the active component in solvents comprising water, ethanol, or propylene glycol are
       examples of liquid compositions suitable for parenteral administration.

       Sterile solutions can be prepared by dissolving the active component in the desired
       solvent system, and then passing the resulting solution through a membrane filter to
20   sterilize it or, alternatively, by dissolving the sterile compound in a previously
       sterilized solvent under sterile conditions.

       In a preferred embodiment of the invention in the compounds claimed, or the
       pharmaceutical acceptable salts or solvates thereof, R_1, R_3 and R_4 are H, R_2 is
25   halogen and preferably iodine over bromine and chlorine and R_5 is H, C_1 to C_8 alkyl
       or C_1 to C_8 substituted alkyl.

       A particularly preferred compound which may act as a partial agonist of LXR is
       shown in formula (II) below (MOLNAME TR1040001892). It has been demonstrated
30   that this compound has a low effective concentration at LXR with an EC_{50} of 2 µM in
       a FRET assay wherein the EC_{50} reflects the half-maximal effective concentration,
       and which is higher than the EC_{50} of 0.015 µM for the published LXR agonist
       TO901317 (J. Schultz et al., Genes Dev. 14, 2831-2838, 2000). Compound
       according to formula (II) does show selective upregulation of ABCA1 and ABCG1 in
35   THP-1 macrophages but does not significantly upregulate FAS and much reduced
       SREBP-1c in HepG2 cells (see EXAMPLE 5 further down).

5

(II)
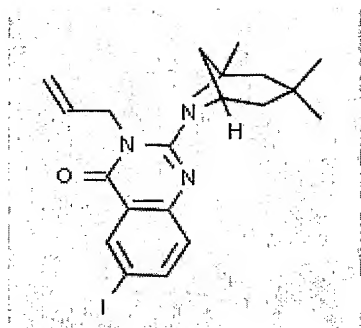
It has also been found that the compound according to formula (III) (Molname
TR1040011382) to be active as partial agonist of the LXR human nuclear receptors
10   with a selective upregulation of the target genes ABCA1 and ABCG1 in THP-1 cells
compared to FAS and SREBP-1c in HepG2 cells.
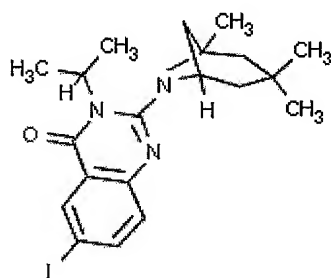
(III)

It has also been found that the compounds according to formulas (IV) (Molname
15   TR1040002211) and (V) (Molname TR1040002212) to be active as partial agonist of
the LXR human nuclear receptors however with a reduced selectivity regarding the
upregulation of the target genes ABCA1 and ABCG1 in THP-1 cells versus FAS and
SREBP-1c in HepG2 cells compared to compounds of formula (II) and (III) (see
EXAMPLE 5 further down)

20
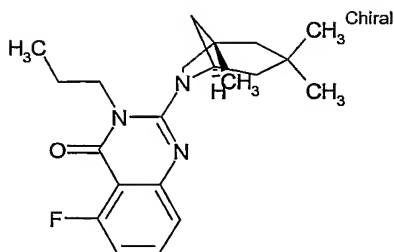
(IV)
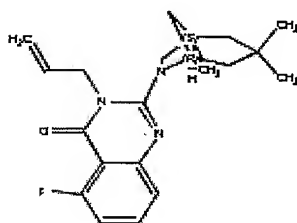
(V)

In particular the invention relates to a compound as described above wherein said compounds is capable of binding the LXR receptor protein or a portion thereof encoded by a nucleic acid according to SEQ ID NO:1 or NO:2 (Fig. 3) or a mammalian homologue thereof. This compound can bind to the LXR receptor protein or a portion thereof in a mixture comprising 10-200 ng of LXR receptor protein, a fusion protein containing LXR or a portion thereof, preferably the ligand binding domain, fused to a Tag, 5-100 mM Tris/HCl at pH 6,8-8,3; 60-1000 mM KCl; 0-20 mM MgCl2; 100-1000ng/µl BSA in a total volume of preferably about 25 µl[see also EXAMPLE 1 and Fig.2).

A mammalian receptor protein homologue of the protein encoded by a nucleic acid according to SEQ ID NO:1 or 2, as used herein is a protein that performs substantially the same task as LXR does in humans and shares at least 40% sequence identity at the amino acid level, preferably over 50 % sequence identity at the amino acid level more preferably over 65 % sequence identity at the amino acid

5   level, even more preferably over 75 % sequence identity at the amino acid level and
     most preferably over 85 % sequence identity at the amino acid level.

     The invention in particular concerns a method for prevention or treatment of a LXR
     receptor protein or LXR receptor protein homologue mediated disease or condition in
10   a mammal comprising administration of a therapeutically effective amount of a
     compound according to the invention wherein the prevention or treatment is directly
     or indirectly accomplished through the binding of a compound according to the
     invention to the LXR receptor protein or to the LXR receptor protein homologue.

15   The term mediated herein means that the physiological pathway in which the LXR
     receptor protein acts is either directly or indirectly involved in the disease or condition
     to be treated or prevented. In the case where it is indirectly involved it could be that,
     e.g. modulating the activity of LXR by a compound according to the invention
     influences a parameter which has a beneficial effect on a disease or a condition. One
20   such example is that modulation of LXR activity leads to decreased levels of serum
     cholesterol or certain lipoproteins which in turn have a beneficial effect on the
     prevention and treatment of atherosclerosis. Herein a condition is a physiological or
     phenotypic state which is desirably altered. One such example would be obesity
     which is not necessarily medically harmful but nonetheless a non desirable
25   phenotypic condition. In a preferred embodiment of the invention the method for
     prevention or treatment of a LXR receptor protein mediated disease or condition is
     applied to a human. This may be male or female.

     Pharmaceutical compositions generally are administered in an amount effective for
30   treatment or prophylaxis of a specific condition or conditions. Initial dosing in human
     is accompanied by clinical monitoring of symptoms, such symptoms for the selected
     condition. In general, the compositions are administered in an amount of active agent
     of at least about 100 µg/kg body weight. In most cases they will be administered in
     one or more doses in an amount not in excess of about 20 mg/kg body weight per
35   day. Preferably, in most cases, doses is from about 100 µg/kg to about 5 mg/kg body
     weight, daily.

5   For administration particularly to mammals, and particularly humans, it is expected
    that the daily dosage level of active agent will be 0,1 mg/kg to 10 mg/kg and typically
    around 1 mg/kg.

    By "therapeutically effective amount" is meant a symptom-alleviating or symptom-
10 reducing amount, a cholesterol-reducing amount, a cholesterol absorption blocking
    amount, a protein and/or carbohydrate digestion-blocking amount and/or a de novo
    cholesterol biosynthesis-blocking amount of a compound according to the invention.

15 Likewise the invention concerns a method of treating in mammal a disease which is
    correlated with abnormal cholesterol, triglyceride, or bile acid levels or deposits
    comprising administering to a mammal in need of such treatment a therapeutically
    effective amount of a compound according to the invention.

20 Accordingly, the compounds according to the invention may also be used in a
    method of prevention or treatment of mammalian atherosclerosis, gallstone disease,
    lipid disorders, Alzheimer's disease, skin disorders, inflammation, obesity or
    cardiovascular disorders such as coronary heart disease or stroke.

25 The invention further concerns a method of blocking in a mammal the cholesterol
    absorption in the intestine in need of such blocking comprising administering to a
    mammal in need of such treatment a therapeutically effective amount of a compound
    according to the invention. The invention may also be used to treat obesity in
    humans.

30

    The Liver X Receptor alpha is a prototypical type 2 nuclear receptor meaning that it
    activates genes upon binding to the promoter region of target genes in a
    heterodimeric fashion with Retinoid X Receptor. The relevant physiological ligands of
    LXR are oxysterols. The compounds have been demonstrated to have a high binding
35 efficacy (binding coefficients measured as EC50 in the range of 1-5 μM) as well as
    agonistic and/or partial agonistic properties. Consequently they may be applied to
    regulate genes that participate in bile acid, cholesterol and fatty acid homeostasis as
    well as other downstream regulated genes. Examples of such genes are but are not

5   limited to lipid absorption, cholesterol biosynthesis, cholesterol transport or binding,
       bile acid transport or binding, proteolysis, amino acid metabolism, glucose
       biosynthesis, protein translation, electron transport, and hepatic fatty acid
       metabolism. LXR often functions in vivo as a heterodimer with the Retinoid X
       Receptor. Published non-steroidal LXR agonists such as the "Tularik" compound

10   "TO901317" (see figure 5) are known to influence the regulation of various liver
       genes. Genes found to be regulated by TO901317 can be found in figure 6. Thus, the
       invention also concerns a method of modulating a gene whose expression is
       regulated by the LXR receptor in a mammal comprising administration of a
       therapeutically effective amount of a compound according to the invention to said

15   mammal.

       A number of direct and indirect LXR target genes have been described whose
       regulated expression contribute to cholesterol homeostasis and lipogenesis. In this
       respect the direct regulation of Cyp7A, which was shown to be a direct target gene of

20   LXR at least in the rodent lineage is an important aspect of cholesterol removal by
       increased metabolism of bile acids (Lehmann et al., J Biol.Chem. 272 (6) 3137-3140;
       1007). Gupta et al. (Biochem. Biophys Res.Com, 293; 338-343, 2002) showed that
       LXR α regulation of Cyp7A is dominant over FXR inhibitory effects on Cyp7A
       transcription.

25

       A key transcription factor that was also shown to be a direct target gene for the LXR
       receptor is SREBP-1C (Repa et al., Genes and Development, 14:2819-2830; 2000:
       Yoshikawa et al.; Mol.Cell.Biol.21 (9) 2991-3000, 2001). SREBP-1C itself activates
       transcription of genes involved in cholesterol and fatty acid synthesis in liver but also

30   other mammalian tissues. Some of the SREBP1c target genes involved in
       lipogenesis like FAS and SCD have shown to be additionally direct targets of the
       LXR receptors (Joseph et al.; J Biol Chem. 2002 Mar 29;277(13):11019-25; Liang et
       al., J Biol Chem. 2002 Mar 15;277(11):9520-8.).

35   A primary limitation for the applicability of LXR agonists as e.g. anti-atherosclerotic
       drugs comes from the observation that compounds with full agonistic activity, e.g.
       TO901317, not only elevate HDL cholesterol levels but do also increase plasma
       triglyceride levels in mice (Schultz et al., 2000 Genes Dev. 14:2831-8.).
       Concomitantly, not only genes that are involved in cholesterol efflux such as the

5   cholesterol transporter ABCA1 (Venkateswaran et al., 2000 PNAS. 97:12097-102.),
        ABCG1 as well as the lipid binding protein Apoliprotein E (Laffite et al. 2001 PNAS
        98:507-512) are induced by full LXR agonists, but also genes involved in
        lipogenesis, including the fatty acid synthase FAS (Joseph et al 2002 J Biol Chem.
        277:11019-11025), and SREB P-1c (Yoshikawa et al., 2001 Mol Cell Biol. 21:2991-

10   3000). Elevation of serum triglyceride levels is an indendent risk factor for
        atherosclerosis (for review see Miller (1999) Hosp Pract (Off Ed) 34: 67-73.). Thus, LXR
        activity needs to be selectively modulated for therapeutic benefit. In particular,
        compounds need to be found that stimulate reverse cholesterol transport, but do not
        significantly increase trigclyceride levels.

15

        Another gene that has been shown to be directly regulated by LXRs is the LPL gene,
        that codes for a key enzyme that is responsible for the hydrolysis of triglycerides in
        circulating lipoprotein, releasing free fatty acids to peripheral tissues. (Zhang et al. J
        Biol Chem. 2001 Nov 16;276(46):43018-24.) This enzyme is believed to promote

20   uptake of HDL cholesterol in liver, thereby promoting reverse cholesterol transport. A
        similar functional involvement in HDL clearance is described for the CETP gene
        product that facilitated the transfer of HDL cholesterol esters from plasma to the liver.
        LXR response elements were found in the CETP promoter and direct activation of
        this gene by LXR was demonstrated (Luo and Tall; J Clin Invest. 2000

25   Feb;105(4):513-20.).

        The regulated transport of cholesterol through biological membranes is an important
        mechanism in order to maintain cholesterol homeostasis. A pivotal role in these
        processes in multiple tissues like e.g. macrophages and intestinal mucosa cells is

30   maintained by the ATP-binding cassette transporter proteins (ABC). ABCA1 and
        ABCG1 were identified as direct LXR target genes (Costet et al.; J Biol Chem. 2000
        Sep 8;275(36):28240-5) that mediate cholesterol efflux and prevent thereby e.g.
        generation of artherogenic plaques in macrophages (Singaraja et al. J Clin Invest.
        2002 Jul;110(1):35-42). Other ABC transporters like ABCG5 and ABCG8 , primarily

35   expressed in hepatocytes and enterocytes have also been reported to be directly
        responsive to LXR agonists (Repa et al., J Biol Chem. 2002 May 24;277(21):18793-
        800. Kennedy et al., J Biol Chem. 2001 Oct 19;276(42):39438-47) and mediate the
        secretion of sterols from the liver and efflux of dietary sterols from the gut .

5   Apolipoproteins E, C-I, C-II, and C-IV, that fulfill important roles in lipoprotein/lipid
     homeostasis have also been shown to be direct targets of the LXR receptor (Laffitte
     et al., Proc Natl Acad Sci U S A. 2001 Jan 16;98(2):507-12; Mak et al.; J Biol Chem.
     2002 May 24 [epub ahead of print]). These proteins have been found to be crucial
     components of chylomicrons, VLDL, IDL, and HDL and are among other things
10   associated with hypertriglyceridemia and arteriosclerosis.

     Recently the LXRα itself was shown to be regulated by both LXR receptors in human
     cell types including macrophages suggesting an autoregulatory amplification event in
     the response to LXR ligands which could e.g. lead to an enhanced stimulation of LXR
15   target genes like e.g. ABCA1 (Bolten et al.; Mol Endocrinol. 2002 Mar;16(3):506-14.;
     Laffitte et al., Mol Cell Biol. 2001 Nov;21(22):7558-68; Whitney et al.; J Biol Chem.
     2001 Nov 23;276(47):43509-15).

     Besides the important function of LXR receptors in tissues like liver and
20   macrophages it has recently been reported that that stimulation of epidermal
     differentiation is mediated by Liver X receptors in murine epidermis. Differentiation
     maker genes like involucrin, loricin and profilaggrin have been shown to be
     upregulated upon LXR ligand treatment (Kömüves et al.; J Invest Dermatol. 2002
     Jan;118(1):25-34.).
25
     Another recent report describes the regulation of cholesterol homeostasis (primarily
     the regulation of ABCA1, ABCG1 and SREBP-1C) by the LXR receptors in the
     central nervous system suggesting that LXRs may prove benefical in the treatment of
     CNS diseases such as Alzheimer's and Niemann-Pick disease that are known to be
30   accompanied by dysregulation of cholesterol balance (Whitney et al.; Mol Endocrinol.
     2002 Jun;16(6):1378-85).

     Activation of LXR by an agonist improves glucose tolerance in a murine model of
     diet-induced obesity and insulin resistance. Gene expression analysis in LXR
35   agonist-treated mice reveals coordinate regulation of genes involved in glucose
     metabolism in liver and adipose tissue, e.g. the down-regulation of peroxisome
     proliferator-activated receptor gamma coactivator-1 alpha (PGC-1),
     phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase

5   expression and induction of glucokinase in liver. In adipose tissue, activation of LXR
       led to the transcriptional induction of the insulin-sensitive glucose transporter,
       GLUT4. LXR agonist may limit hepatic glucose output and improve peripheral
       glucose uptake (Laffitte et al. (2003) PNAS 100:5419-24).

       Therefore one other important embodiment of the invention concerns methods that
10   enhances or suppresses amongst other today yet unknown LXR target genes the
       above mentioned genes and the associated biological processes and pathways
       through LXR compounds that are subject of this invention.

       The compounds according to the invention may be used as medicaments, in
15   particular for the manufacture of a medicament for the prevention or treatment of a
       LXR receptor protein or LXR receptor protein homologue mediated disease or
       condition in a mammal wherein the prevention or treatment is directly or indirectly
       accomplished through the binding of the compound according to the invention to the
       LXR receptor protein or LXR receptor protein homologue. These pharmaceutical
20   compositions contain 0,1 % to 99,5 % of the compound according to the invention,
       more particularly 0,5 % to 90 % of the compound according to the invention in
       combination with a pharmaceutically acceptable carrier.

       The invention concerns also the use of a compound according to the invention for the
25   manufacture of a medicament for the prevention or treatment of a LXR receptor
       protein mediated disease or condition wherein the mammal described above is a
       human. The medicament may be used for regulating the cholesterol transport
       system, for regulating levels of cholesterol, triglyceride, and/or bile acid in a mammal
       preferentially a human by activating the LXR receptor. The medicament may be used
30   for the treatment of atherosclerosis, gallstone disease, lipid disorders, Alzherimer's
       disease, skin disorders, obesity or a cardiovascular disorder.

       The invention further concerns the use of a compound according to the invention for
       the manufacture of a medicament capable for blocking in a mammal, preferentially in
35   a human the cholesterol absorption in the intestine. Further the claimed compound
       may be used for the manufacture of a medicament for treating obesity in humans and

5   for modulating a gene whose expression is regulated by the LXR receptor (see

details above and figures).

EXAMPLES

EXAMPLE 1

In vitro screening for compounds which influence LXR binding to coactivators.

For screening purposes a GST and 6 x His fusion of the LBD (from amino acids 155 of hLXRalpha to 447) of human LXRalpha is constructed by first cloning a Gateway cassette (Invitrogen) in frame into the Sma I site of the pAGGHLT Polylinker (Pharmingen). Then a PCR fragment specifically amplified from human liver cDNA is cloned into the resulting pACGHLT-GW following the manufacturers instructions for Gateway cloning (Invitrogen) to yield pACGHLT-GW-hLXRalphaLBD.
Primers used for Amplification are:
GGGGACAAGTTTGTACAAAAAAGCAGGCTCGCTTCGCAAATGCCGTCAG and
GGGGACCACTTTGTACAAGAAAGCTGGGTCCCCTTCTCAGTCTGTTCCACTT .
100 % sequence integrity of all recombinant products is verified by sequencing.
Recombinant Baculovirus is constructed from pACGHLT-GW-hLXRalphaLBD using the Pharmingen Baculovirus Expression vector system according to instructions of the manufacturer. Monolayer cultures of SF9 cells are infected by the virus as recommended by Pharmingen or 200ml cultures of 1 x10^6 cells/ml grown in 2 liter Erlenmeyer flasks on an orbital shaker at 30 rpm are infected by 10ml of same virus stock. In both cases cells are harvested 3 days after infection. All cell growth is performed in Gibco SF900 II with Glutamine (Invitrogen) medium without serum supplementation at 28°C. Since SF9 cells contain significant amounts of endogenous GST, purification is performed via His and not via GST affinity chromatography. To this end instructions of Pharmingen for purification of recombinant His tagged proteins from SF9 cells are followed with the following modifications: All detergents are omitted from the buffers and cells were lysed on ice by 5 subsequent sonication pulses using a sonicator needle at maximum power.
All eluates are dialyzed against 20 mM Tris/HCl pH 6,8, 300 mM KCl; 5 mM MgCl$_2$; 1 mM DTT; 0,2 mM PMSF; 10% Glycerol. A typical dialyzed eluate fraction contains the fusion protein at a purity of more than 80%. Total protein concentration is 0,1-0,3 mg/ml.

For E. coli expression of a NR coactivator, pDest17-hTif2BD expressing a NR interaction domain from amino acids 548-878 of human Tif2 (Acc. No: XM_011633 RefSeq) tagged by 6 N-terminal His residues is constructed. Therefore, a PCR fragment specifically amplified from human liver cDNA is subcloned into pDest 17 (Invitrogen) following the manufacturers instructions for Gateway cloning (Invitrogen).Primers used for Amplification are:

GGGGACAAGTTTGTACAAAAAAGCAGGCTCGTTAGGGTCATCGTTGGCTTCACC and

GGGGACCACTTTGTACAAGAAAGCTGGGTCTCAAAGTTGCCCTGGTCGTGGGT TA

For E. coli expression plasmid DNA is transformed into chemically competent E. coli BL21 (Invitrogen, USA) and cells are grown to an OD600 of 0.4-0.7 before expression was induced by addition of 0,5 mM IPTG according instructions of the manufacturer (Invitrogen). After induction for 8 hours at 30°C cells are harvested by centrifugation for 10 minutes at 5000 x g. Fusion proteins are affinity purified using Ni-NTA Agarose (QIAGEN) according to the instructions of the manufacturer. Recombinant Tif2 construct is dialyzed against 20 mM Tris/HCL pH 7.9; 60 mM KCl; 5 mM MgCl$_2$; 1 mM DTT, 0,2 mM PMSF; 10% glycerol. A typical dialyzed eluate fraction contains the fusion protein at a purity of more than 80%. Total protein concentration is 0,1-0,3 mg/ml.

The TIF2 fragment is subsequently biotinylated by addition of 5-40µl/ml Tif2 fraction of a Biotinamidocaproate N-Hydroxysuccinimide-ester (Sigma) solution (20 mg/ml in DMSO). Overhead rotating samples are incubated for 2 hours at room temperature. Unincorporated label is then separated using G25 Gel filtration chromatography (Pharmacia Biotech, Sweden). Protein containing fractions from the column are pooled and tested for activity in the assay as described below.

For screening of compound libraries as provided for by the methods shown below in the examples for substances which influence the LXR/Tif 2 interaction, the Perkin Elmer LANCE technology is applied. This method relies on the binding dependent energy transfer from a donor to an acceptor fluorophore attached to the binding partners of interest. For ease of handling and reduction of background from compound fluorescence LANCE technology makes use of generic fluorophore labels and time resoved detection (for detailed description see Hemmilä I, Blomberg K and

Hurskainen P, Time-resolved resonance energy transfer (TR-FRET) principle in LANCE, Abstract of Papers Presented at the 3 rd Annual Conference of the Society for Biomolecular Screening, Sep., California (1997))

For screening, 20-200 ng of biotinylated Tif 2 fragment and 10-200 ng of GST-LXR fragment are combined with 0.5-2 nM LANCE Eu-(W1024) labelled anti-GST antibody (Perkin Elmer) and 0,1-0,5µg of highly fluorescent APC-labelled streptavidin (Perkin Elmer, AD0059) in the presence of 50µM of individual compounds to be screened in a total volume of 25 µl of 20 mM Tris /HCl pH 6,8; 300 mM KCl; 5 mM MgCl2; 100-1000 ng/µl/ BSA DMSO content of the samples is kept below 4%. Samples are incubated for a minimum of 60 minutes in the dark at room temperature in FIA-Plates black 384well med. binding (Greiner).

The LANCE signal is detected by a Perkin Elmer VICTOR2V™ Multilabel Counter applying the detection parameters listed in Fig. 2. The results are visualized by plotting the ratio between the emitted light at 665 nm and at 615 nm. For every batch of recombinant proteins amount of proteins, including BSA and labeling reagents giving the most sensitive detection of hits is determined individually by analysis of dose response curves for 22R Hydroxycholesterol and TO 901317

EXAMPLE 2

Experimental procedure for the preparation of the compounds according to the invention.

o-AZIDOBENZOIC ACID SYNTHESIS (2)

The anthranilic acid (1, 1 eq., 0.5-1 M) is suspended in 6 M HCl, containing enough AcOH (0-20% dependent upon the anthranilic acid) to facilitate dissolution of the anthranilic acid and/or the intermediate diazonium salt, and cooled to 0 °C. NaNO$_2$ (1.1 eq., 1.3-2.5 M) dissolved in H$_2$O is added to the anthranilic acid solution at a rate such that the temperature of the reaction solution remains below 5 °C. The resulting homogeneous solution of the diazonium salt is slowly filtered through a sintered glass funnel into a solution of NaN$_3$ (1.1 eq., 0.7-1.1 M) and NaOAc (12 eq.) in H$_2$O. The

reaction mixture is stirred/shaken for 30-60 min following cessation of vigorous N_2 evolution. Following acidification of the reaction mixture to pH 1 with concentrated HCl, the mixture was cooled to 0 °C to encourage complete precipitation of the *o*-azidobenzoic acid. The precipitate is collected by filtration and washed with 6 M HCl (2x) and H_2O (2x). The *o*-azidobenzoic acid product (2) is dried *in vacuo* (500 mtorr, 30 °C).

ACYLATION OF HYDROXYMETHYL RESIN (4)

To hydroxymethyl resin (1.0 eq., 1.3 mmol/g) and the *o*-azidobenzoic acid (1, 2.5 eq.) is added DMF (to give 400 mM *o*-azidobenzoic acid ,1), $CsCO_3$ (2.0 eq.) and KI (2.0 eq.). Following agitation of the reaction mixture for 36-48 h, the resin-bound *o*-azidobenzoic acid (4) is washed with MeOH (2 cycles), CH_2Cl_2 (3 cycles), MeOH (3 cycles), DMF (3 cycles), MeOH (3 cycles) and CH_2Cl_2 (3 cycles), and dried *in vacuo*.

AZA-WITTIG FORMATION (5)

To the resin-bound *o*-azidobenzoic acid (4,1.0 eq.) is added a solution of PPh_3 (THF, 500 mM, 5.0 eq.). After 6 h, the resin is washed with 3 cycles of the following: THF (3 cycles), toluene (3 cycles), CH_2Cl_2 (3 cycles) and hexanes (3 cycles). Followed by drying *in vacuo* to afford resin bound iminophosphorane (5)

CARBODIIMIDE FORMATION (6)

To the resin-bound iminophosphorane (5, 1 eq.) is added isocyanate (9 , 5 eq., 450 mM) dissolved in $ClCH_2CH_2Cl$. The compounds are shaken at ambient temperature for 16 h, washed with 3 cycles of the following: THF (3 cycles), toluene (3 cycles), CH_2Cl_2 (3 cycles) and hexanes (3 cycles), and dried *in vacuo* to afford carbodiimide (6).

GUANIDINE FORMATION / CYCLIZATION

To the carbodiimide functionalized resin (6) is added secondary amine (10, 0.6 eq., 500 mM) dissolved in ClCH$_2$CH$_2$Cl. The reaction mixture is heated to 50 °C in an incubator for 12-72 h to afford 2-aminoquinazoline (8).

All of the final products are analyzed using an Evaporative Light Scattering Detector (ELSD) detection to determine purity.

EXAMPLE 3

This example illustrates that compounds according to the invention (experiments shown were done with MOLSTRUCTURE TR1040001892, TR1040011382 , TR1040002211 and TR1040002212 (see formulas (II) to (V) for structural formulas)) activate luciferase reporter gene expression in a dose dependent manner mediated through GAL4-LXRa-LBD or GAL4-LXRb-LBD constructs in HEK293 cells. TR1040001892 and TR1040011382 do activate LXR beta LBD truct mediated luciferase activity much stronger than with LXR alpha construct which is in contrast to the similar activation of both LXR alpha and LXR beta LBD containing constructs by TR1040002211 and TO901317.

HEK293 cells are grown in 96 well plates and co-transfected with pFR-luc (Stratagene) and pCMV-BD-LXRa-LBD or pCMV-BD-LXRb-LBD (each 100 ng of plasmid DNA per well). Transfection is carried using Lipfectamine 2000 (Gibco-BRL) according to the manufacturers protocol. The ligand binding domains (LBD) of LXRa and LXRb are cloned into the pCMV-BD-GW (the Gateway Reading Frame Cassette B is cloned as an EcoRV fragment into SmaI site of pCMV-BD) applying the manufacturer protocols for the Gateway^{TM} system (Invitrogen).

Luciferase reporter activity is measured in triplicates from extracts of cells after incubating cells in culture medium (DMEM [Gibco-BRL] + 10% FCS [PAA laboratories]) for 16 hours (5% CO$_2$, 37^{0}C) containing 0,5% DMSO (control) or 0,5% DMSO with increasing concentrations of TR1040001892, TR1040002211 or T0901317 (Sigma T 2320, see figure 5 for structural formula). The type of assay used here is a mammalian one hybrid (M1H) assay that is known to those skilled in the art.

Dose-dependent luciferase activities originating from pFR-luc demonstrate the relative activities of the compounds with the LXRa or LXRb LBDs in this mammalian one hybrid type approach.

EXAMPLE 4

This example shows that described compounds can increase the abundance of mRNA of LXR target genes like ABCA1 and ABCG1 in THP-1 cells which are treated with TPA or FAS and SREBP-1c in HepG2 cells as shown in Fig 8A-D.

THP-1 cells are seeded in 24 well plates at 3 $x10^5$ cells per well in RPMI 1640 medium containing 10 % FCS and 100 nM TPA for 24 h. HepG2 cells are seeded in poly-L-Lysine coated 24well plates at 1x10^6 cells per well in EMEM medium containing 10 % FCS until they are appr. 60% confluent.

Before treatment with LXR compounds, the growth medium is changed to medium containing 10% charcoal/dextran-stripped FCS for 12 h. Treatment is done for 12h (THP-1 cells) and 24h (HepG2 cells), respectively, in medium containing 10% charcoal/dextran-stripped FCS (and 100 nM PMA in the case of THP-1 cells).

LXR compounds are dissolved in DMSO, with the final solvent concentration never exceeding 0.125% . All treatments are done in triplicates and experiments repeated twice. Total RNA is extracted using the Qiagen Rneasy Mini Kit and treated with DNase (DNAfree kit, Ambion). RNA is reverse transcribed with Oligo(dT) primer and real-time reverse transcription PCR (TaqMan) is performed using the ABI Prism 7900HT Sequence Detection System and reagents supplied by Applied Biosystems. mRNA steady state levels are normalised to H3 histone (H3F3A) expression levels.

The sequences of forward primers, reverse primers and TaqMan probes are as follows :

FAS : CTGAGACGGAGGCCATATGCT, GCTGCCACACGCTCCTCTAG, FAM-CAGCAGTTCACGGACATGGAGCACAA-TAMRA
ABCA1 :TCCTGTGGTGTTTCTGGATGAAC, CTTGACAACACTTAGGGCACAATTC, FAM- ACCACAGGCATGGATCCCAAAGCC-TAMRA

EXAMPLE 5

All compounds T0901317, TR1040002211, TR1040002212. TR1040001892, TR1040011382, LN0000006662 and LN0000006674 cause a marked increase in cholesterol export in differentated THP-1 macrophages (see Figure 9 A).

Strikingly, the compound T0901317 causes a marked increase in triyglyceride mass in HepG2 liver cells, while compounds like TR1040001892 and TR1040011382 do not cause a significant increase in triglyceride mass. Compounds TR1040002211 and TR1040002212 cause a slight increase in triglyceride mass.

This behavior is similar to the selective transcriptional effect of compounds like TR1040001892 and TR1040011382 on the LXR target genes in HepG2 versus THP-1 cells.

Methods: Cultures of the monocyte-macrophage cell line and the hepatocytes HepG2 are obtained from the American Type tissue Culture Collection, Rockville, MD and were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum, 10 mM HEPES, 2 mM Pyruvat, 50 µM ß-Mercaptoethanol (THP-1) and Minimum essential medium (Eagle) with 2 mM L-glutamine and Earle's BSS supplemented with 10% fetal bovine serum, 2 mM glutamine, 0.1 mM non-essential amino acids, 1 mM sodium pyruvate (HepG2), respectively, at 37°C in 5% CO2.

THP-1 cells are differentiated into macrophages by addition of 100 nM Phorbol 12-Myristate 13-Acetate (PMA; Sigma P8139) and PMA included in the medium of all subsequent experiments to maintain differentiation.

For cholesterol efflux measurements and triglyceride analysis cells are seeded in 6well plates at 1.8x106 cells (THP-1) and 1x106 cells (HepG2) per well, respectively.

CHOLESTEROL EFFLUX

THP-1 cells are seeded in 6well plates at $1X10^6$ cells per well in RPMI 1640 medium containing 10 % FCS and 100 nM TPA for 72 h. After washing with PBS cells are incubated 24 h with fresh in RPMI 1640 medium containing 10 % FCS and 100 nM TPA. Cells are washed twice with PBS and RPMI 1640 medium containing 0.15% BSA and 100 nM TPA is added for further 24 h. Treatment with LXR compounds is done for 24 h in RPMI 1640 medium containing 0.15% BSA, 100 nM TPA and 40

μg/ml ApoA1 (Calbiochem # 178452). Medium is collected, centrifuged to remove cell debris and assayed for cholesterol using a commercial fluorometric kit (Molecular Probes A-12216). The remaining cellular proteins are lysed with 0.3 N NaOH and protein content measured with the Biorad Bradford reagent.

TRIGLYCERIDE ASSAY

HepG2 cells are seeded in poly-L-Lysine coated 6well plates at 1×10^6 cells per well in EMEM medium containing 10 % FCS until they were appr. 60% confluent. Before treatment with LXR compounds growth medium is changed to medium containing 10% charcoal/dextran-stripped FCS for 12 h. Treatment is done for 24h in medium containing 10% charcoal/dextran-stripped FCS. Cells are washed twice with ice-cold PBS/0.2% BSA and twice with cold PBS and all liquid carefully removed. Triglyceride are extracted with with 1.5 ml hexane/ isopropanol = 3:2 per well with gentle shaking for 2-3 h at RT according to Pan et al. (2002) JBC <u>277</u>, 4413-4421 and Goti et al. (1998) Biochem J, <u>332</u> , 57-65 . The extraction solution is collected, dried under vacuum and redissolved in isopropanol/ 1.5% triton. The remaining cellular proteins are lysed with 0.3 N NaOH and protein content measured with the Biorad Bradford reagent.

Triglyceride levels are measured as esterified glycerol using a commercial enzymatic colorimetric kit (Sigma 343-25P). In a preliminary assay it is checked by omitting the lipase enzyme that contribution of free glycerol is negligible.

FIGURE CAPTIONS

FIG. 1

Fig. 1 shows the synthesis of the compounds according to the invention as also described in EXAMPLE 2.

FIG. 2

Fig. 2 shows the measurement parameters employed by the Wallace VICTOR2V™ Multilabel Counter which was used for measuring the EC_{50} values (see also EXAMPLE 1)

FIG. 3

Shows a table with the accession numbers for the key genes

FIG. 4

Fig. 4 shows the internal molecular name used by the applicant (MOLNAME) as well as the corresponding structures of preferred compounds according to the invention. The figure further shows their respective EC_{50} values (EC50 AVG) as established according to the Example 1 in multiple experiments (see above), as well as their respective average efficacy (% activity relative to TO901317 control agonist).

FIG. 5

Figure 5 shows various known LXR ligands. The compound TO901317 is used as a reference compound here. It is apparent from their structures that the inventors have identified novel compounds which are structurally not related to these known ligands.

FIG. 6

Figure 6 shows various genes that have been found to be regulated through binding of an LXR agonist to the LXR protein.

FIG. 7

Fig 7A and Fig 7B show dose dependence of inidcated compounds with LXR alpha LBD (7A) or LXR beta (7B) LBD containing constructs in mammalian one hybrid (M1H) type assays. The respective µM concentrations of the compounds T0901317,

TR1040002211, TR1040002212. TR1040001892 and TR1040011382 are given on the x-axis and the relative light units (RLU) are depicted on the y-axis.

Fig. 8

Analysis of mRNA content of the indicated genes (ABCA1, ABCG1, FAS and SREBP-1c) in total RNA isolated from THP-1 cells (8A and 8B) or HepG2 cells (8C and 8D) treated for 12 or 24 hours with indicated concentrations (µM on x-axis) of T0901317, TR1040011382, TR1040001892 and TR1040002211. The relative fold inuction is depicted on the y-axis.

Fig. 9

Analysis of relative fold increase in total cholesterol from supernatants of cultivated THP-1 cells (indicated on the y-axis) incubated with ApoA1 and with or without 10µM of the compounds T0901317, TR1040002211, TR1040002212. TR1040001892, TR1040011382, LN0000006662 and LN0000006674 as indicated on the X-axis of Fig 9A.

Analysis of relative levels of total triglyceride (TG) content in HepG2 cells (indicated on the y-axis) treated with 25µM of the indicated compounds T0901317, TR1040002211, TR1040002212. TR1040001892, TR1040011382, LN0000006662 and LN0000006674 (indicated on the x-axis).

Claims:

1.   A compound of the formula (I), or pharmaceutically acceptable salts or
solvates thereof,

(I)
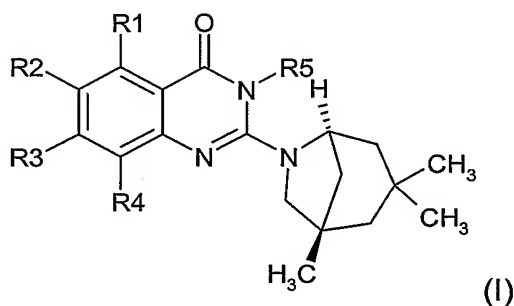
wherein substituents and indices have the following meanings:

R_1, R_2, R_3, R_4, - independent from each other - is H, halogen, hydroxy,
protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to
C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl,
C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected
carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected
amino, (monosubstituted)amino, protected (monosubstituted)amino,
(disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6
alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6
alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-
(phenylsulfonyl)amino or phenyl,

R_5 is H, C_1 to C_8 alkyl, C_2 to C_6 alkenyl, C_1 to C_8 substituted alkyl, C_7 to C_{12}
alkylphenyl or C_7 to C_{12} substituted phenylalkyl.

2.   A compound of the formula (I), or pharmaceutically acceptable salts or
      solvates thereof,

(I)
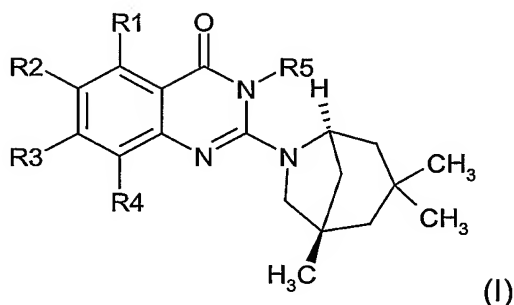
      wherein the substituents and indices have the following meanings:

      R_1, R_3 and R_4 are H, R_2 is halogen, hydroxy, protected hydroxy, cyano, nitro,
      C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted
      alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy,
      protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl,
      protected hydroxymethyl, amino, protected amino, (monosubstituted)amino,
      protected (monosubstituted)amino, (disubstituted)amino, carboxamide,
      protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6
      alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1
      to C_6 alkyl)sulfonyl)amino, N- (phenylsulfonyl)amino or phenyl,
      and R_5 is H, C_1 to C_8 alkyl,
      C_2 to C_6 alkenyl ,C_1 to C_8 substituted alkyl.

3.   A compound according to claim 1 or 2 with: R_1, R_3 and R_4 being H, R_2 being
      halogen and preferably iodine over bromine and chlorine and R_5 being H, C_1 to
      C_6 alkyl, C_3 to C_5 alkenyl, C_1 to C_6 substituted alkyl.

4.   A compound according to any of claims 1 to 3 being

(II)
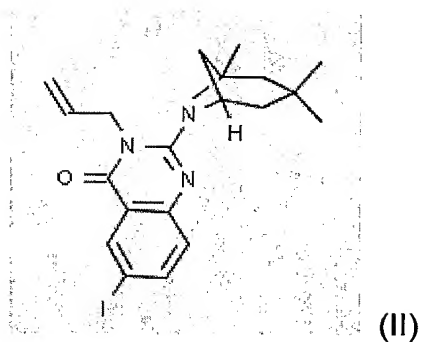
5. A compound according to any of claims 1 to 3 being

(III)
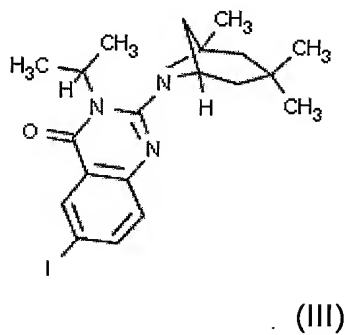
6.   A compound according to claim 1 being

(IV)
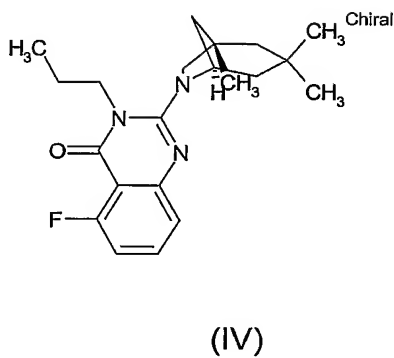
7. A compound according to claim 1 being
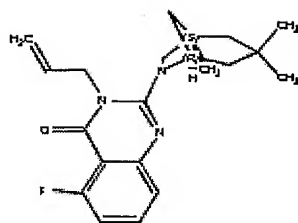
(V)

8. A compound according to any of claims 1 to 3 being
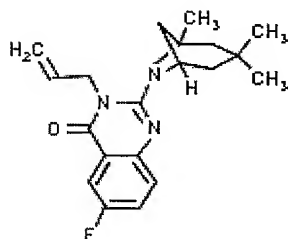
(VI)

9. A compound according to claim 1 or 2 being
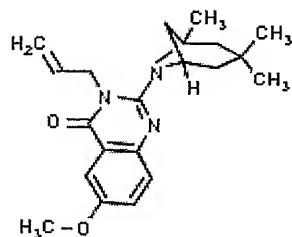
(VII)

10. A compound of according to any of claims 1 to 9 wherein said compound is capable of binding the NR1H3 receptor protein encoded by a nucleic acid comprising SEQ ID NO:2 or a portion thereof or a mammalian homologue thereof .

11. A compound of according to any of claims 1 to 9 wherein said compound is capable of binding the NR1H2 receptor protein encoded by a nucleic acid comprising SEQ ID NO:1 or a portion thereof or a mammalian homologue thereof.

12. A compound according to any of claims 1 to 9 for use as a medicament.

13. A method for prevention or treatment of a NR1H3 and/or NR1H2 receptor protein mediated disease or NR1H3 and/or NR1H2 receptor protein homologue mediated disease or condition in a mammal comprising administration of a therapeutically effective amount of a compound according to claims 1 to 9 wherein the prevention or treatment is directly or indirectly accomplished through the binding of the compound according claims 1 to 9 to the NR1H3 and/or NR1H2 receptor proteins or to the NR1H3 and/or NR1H2 receptor protein homologues.

14. A method for regulating the cholesterol synthesis or transport in a mammal which comprises activating the NR1H3 and/or NR1H2 receptors with a therapeutically effective amount of a compound according to claims 1 to 9.

15. A method of treating in mammal a disease which is affected by cholesterol, triglyceride, bile acid, glucose or glucocorticoid levels comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to claims 1 to 9.

16. A method of treating in a mammal Atherosclerosis, Alzheimers disease, Type II diabetes, lipid disorders, obesity, an inflammatory or a cardiovascular

disorder comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to claims 1 to 9.

17. A method according to any of claims 13 to 16 wherein the expression of one or more of the genes out of the group comprising ABCA1, ABCG1, ABCG5, ABCG8, apolipoprotein-CI, -CII, -CIV, -E, LPL (lipoprotein lipase), CETP (cholesteryl ester transfer protein) or other genes that positively regulate cholesterol homeostasis is increased upon compound administration.

18. A method according to any of claims 13 to 16 wherein the expression of one or more of the genes out of the group comprising 11-ß-HSD (11-ß hydroxysteroid dehydrogenase), PEPCK (phosphoenolpyruvat carboxykinase), G-6-P (glucose-6-phosphatase) is reduced upon compound administration.

19. A method according to any of claims 13 to 16 wherein the expression of one or more of the genes out of the group comprising FAS (Fatty Acid Synthase), SREBP-1c (Sterol-response element binding protein), SCD-1 (Stearoyl-CoA Desaturase), Angiopoietin like protein 3 (Angptl3) or other genes which are relevant for controlling serum triglyceride or glucose levels are not or more weakly increased in liver and or other organs compared to administration of a full agonist like TO901317.

20. A method of blocking in a mammal the cholesterol or fatty acid absorption in the intestine of a mammal in need of such blocking comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to claims 1 to 9.

21. A method for treating obesity in a mammal comprising administring a therapeutically effective amount of a compound according to any of claims 1 to 9.

22. A method of modulating a gene whose expression is regulated by the NR1H3 and/or NR1H2 receptor in a mammal comprising administering a therapeutically effective amount of a compound according to claims 1 to 9.

23. A method according to any of claims 13 to 19 wherein the expression of ABCA1 and/or ABCG1 and/or ABCG5 and/or ABCG8 are increased.

24. Use of a compound according to any of claims 1 to 9 in a method according to claims 13 to 23 wherein the mammal is a human

25. Use of a compound according to any of claims 1 to 9 for the manufacture of a medicament for the prevention or treatment of a NR1H3 and/or NR1H2 receptor protein or NR1H3 and/or NR1H2 receptor protein homologue mediated disease or condition in a mammal wherein the prevention or treatment is directly or indirectly accomplished through the binding of the compound to the NR1H3 and/or NR1H2 receptor protein or NR1H3 and/or NR1H2 receptor protein homologue.

26. Use of a compound according to any of claims 1 to 9 for the manufacture of a medicament for prevention or treatment of a NR1H3 and/or NR1H2 receptor protein mediated disease or condition wherein the mammal is a human.

27. Use of a compound according to any of claims 1 to 9 for the manufacture of a medicament for regulating the cholesterol transport system in a mammal by activating the NR1H3 and/or NR1H2 receptor.

28. Use of a compound according to any of claims 1 to 9 for the manufacture of a medicament for regulating levels of cholesterol, triglyceride, and/or bile acid.

29. Use of a compound according to any of claims 1 to 9 for the manufacture of a medicament for treating in a mammal atherosclerosis, alzheimer disease, gallstone disease, lipid disorders, inflammatory disorder, type II diabetis, obesity or a cardiovascular disorder.

30. Use of a compound according to any of claims 1 to 9 for the manufacture of a medicament capable for blocking in a mammal the cholesterol and/or fatty acid absorption in the intestine.

31. Use of a compound according to any of claims 1 to 9 for the manufacture of a medicament for treating obesity in a mammal.

32. Use of a compound according to any of claims 1 to 9 for the manufacture of a medicament for modulating a gene whose expression is regulated by the NR1H3 and/or NR1H2 receptor.

33. Use of a compound according to any of claims 1 to 9 in a mammal for the selective up-regulation of one or more genes selected from the group comprising ABCA1, ABCG1, ABCG5, ABCG8, apolipoprotein-CI, -CII, -CIV, -E, LPL (lipoprotein lipase), CETP (cholesteryl ester transfer protein) or other genes that positively regulate cholesterol homeostasis are increased and a weaker regulation of one or more of the genes selected from the group comprising FAS and SREBP-1c or other genes that positively regulate lipogenesis, said compound showing a larger difference in regulation of the two groups of genes when compared with the regulatory behaviour of a full agonist like T0901317 on both groups of genes.

34. Use of a compound according any of claims 1 to 9 in a use according to claims 25 to 33 wherein the mammal is human.

Fig.1
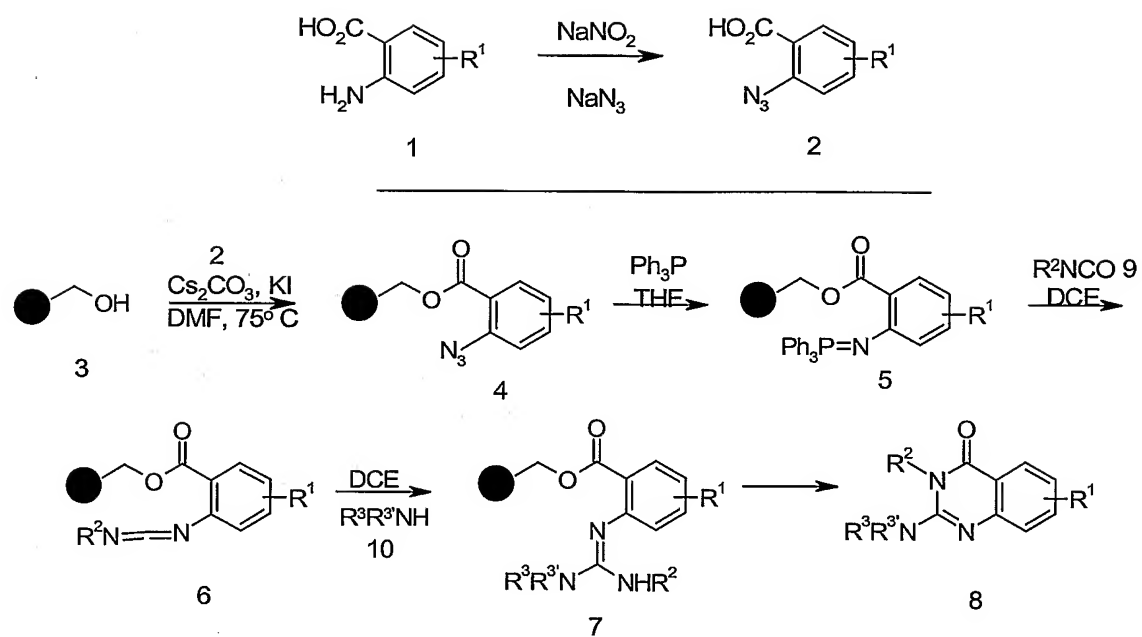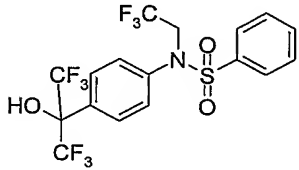
Fig. 2
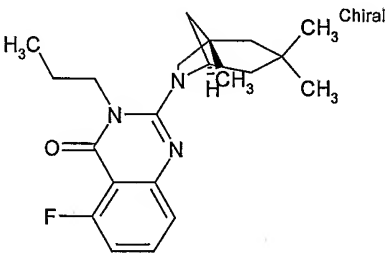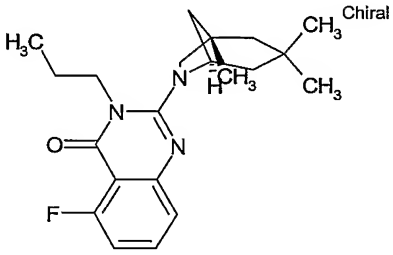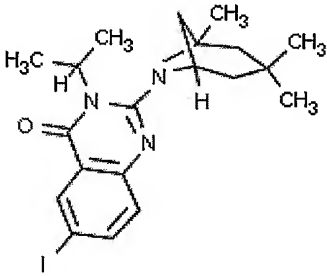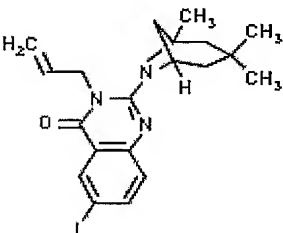
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plate: GREINER FIA-Plate black 384 well med. binding
Measurement height .... 3.50 mm
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Emission filter name D615
Emission filter slot A1
Emission aperture .... Normal
Excitation filter D340
Delay .... 50 µs
Window time .... 400 µs
Cycle .... 1000 µs
Light integrator capacitors 1
Light integrator ref. level 95
Flash energy area .... High
Flash energy level 223
Flash absorbance measurement ...... No
Beam .... Normal
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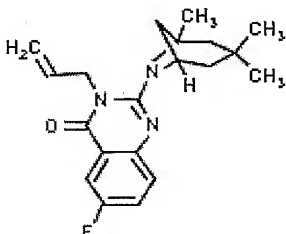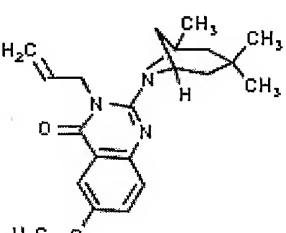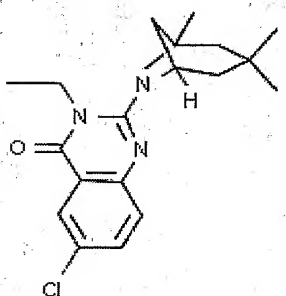
Fig. 3

Gene definition	NCBI Accession number of gene	Corresponding SEQ ID Number
Liver X receptor beta NR1H2	NM_007121	1
Liver X receptor alpha NR1H3	NM_005693	2
Steroid receptor coactivator 1	U90661	3

Fig. 4 A

MOLNAME	MOLECULE STRUCTURE	EC50 AVG [µM]	EFF AV
TO901317	TO901317	0,1	10

MOLNAME	MOLECULE STRUCTURE	EC50 AVG (µM)	%EF AV
TR1040002211		1,5	5(
TR1040002212		4	7!
TR1040011382		12	8(
TR1040001892		4	5(

LN0000006662		4	60
LN0000006674		5	20
LN0000007460		5	50

Fig. 5

TO901317

TO314407
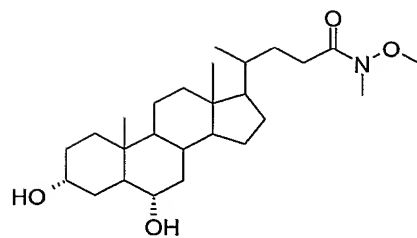
Hypocholamide
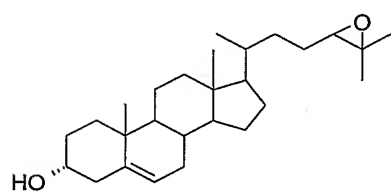
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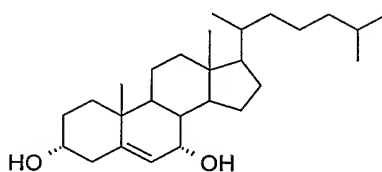
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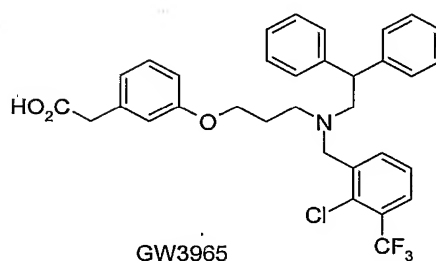
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Fig. 6

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Fig. 7A

Fig. 7B

Fig. 8A

Fig. 8B

Fig. 8C

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- ▲ TR1040011382
- ▼ TR1040001892
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Fig. 8D

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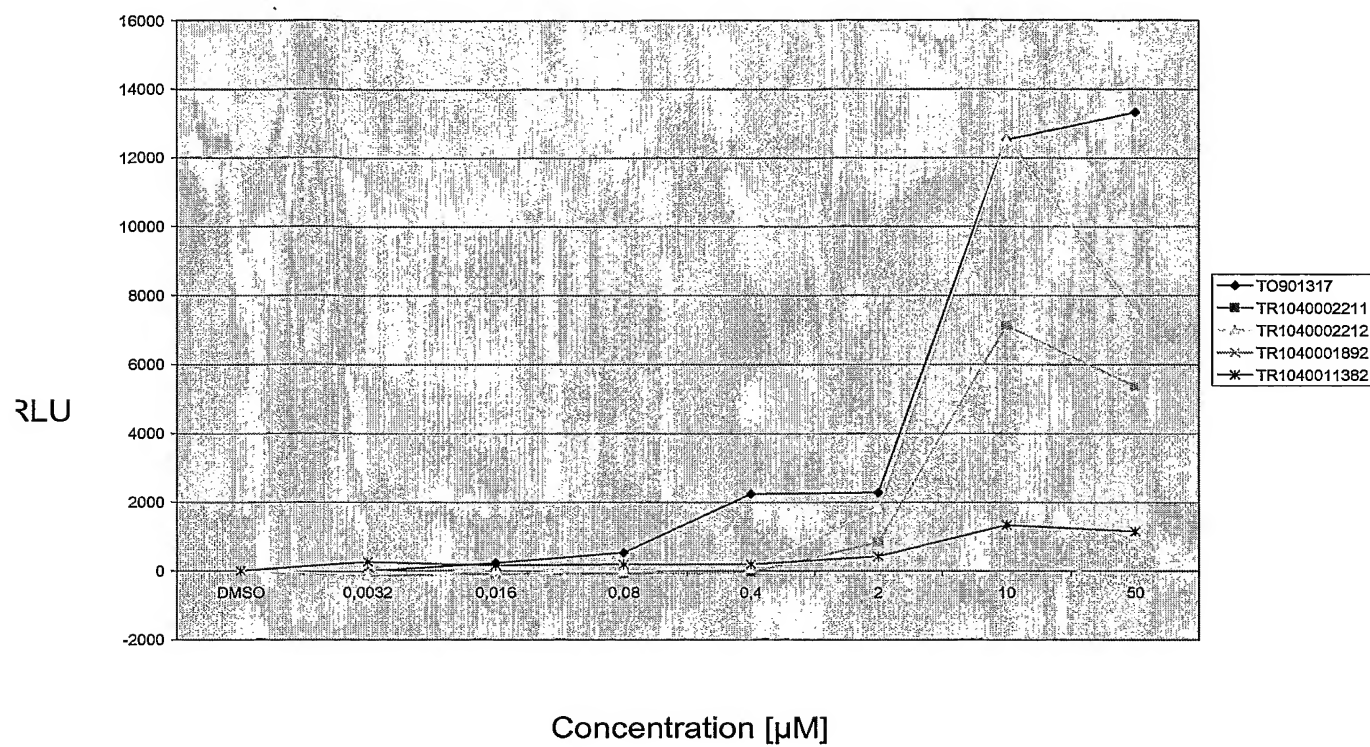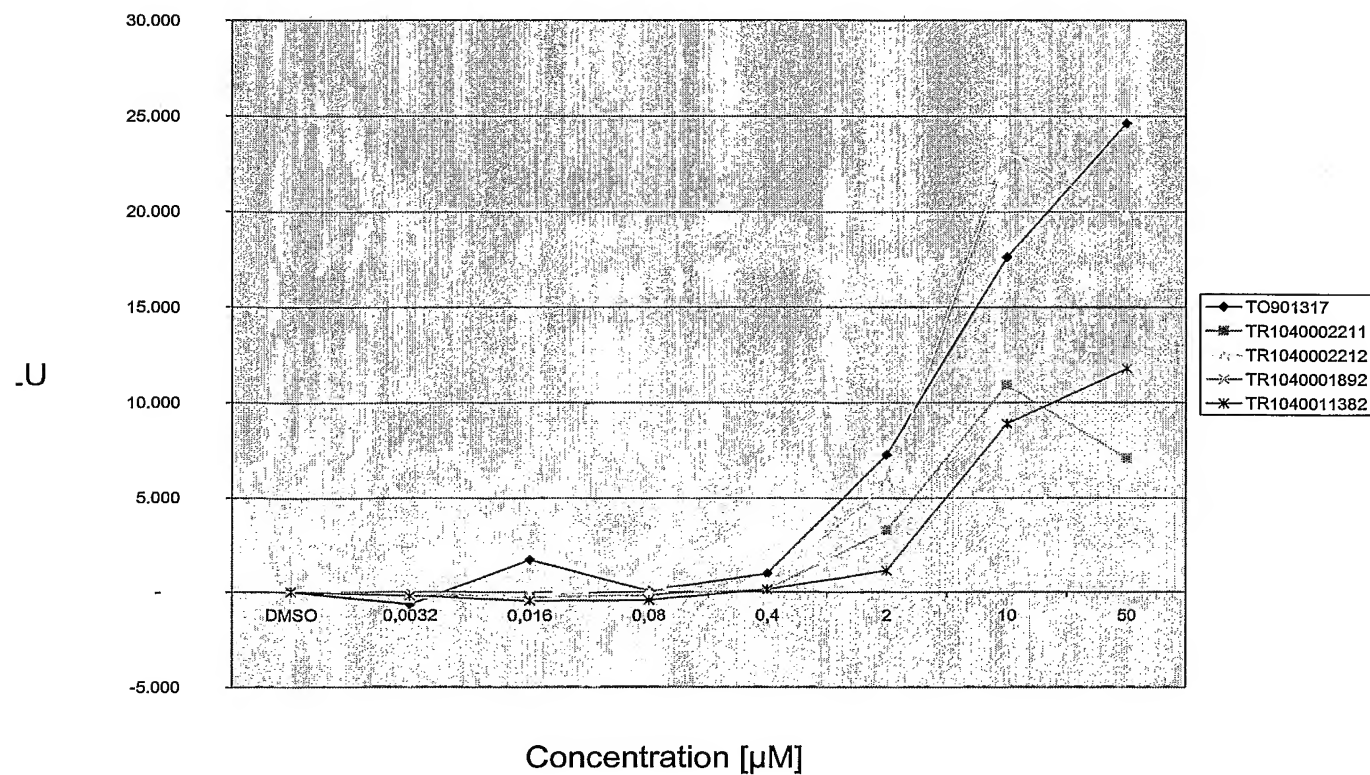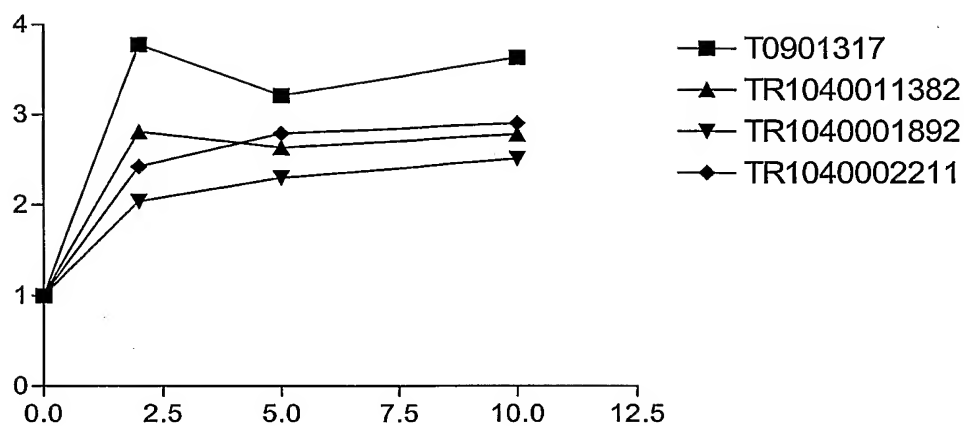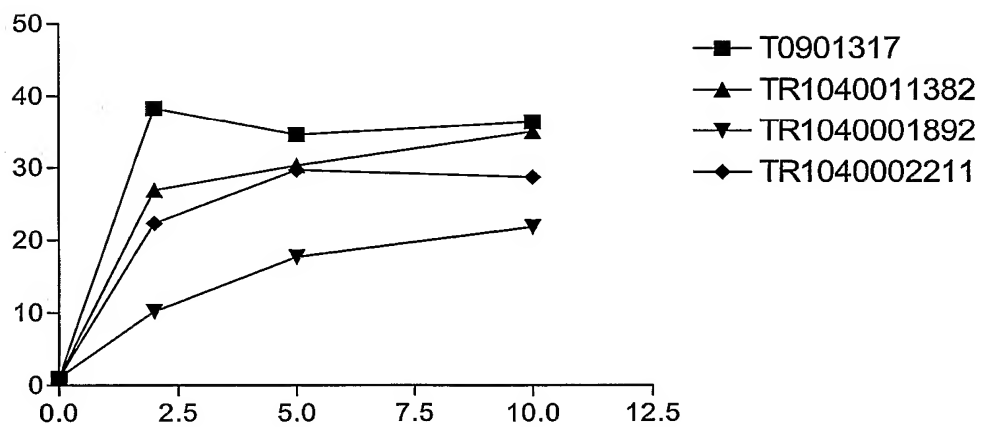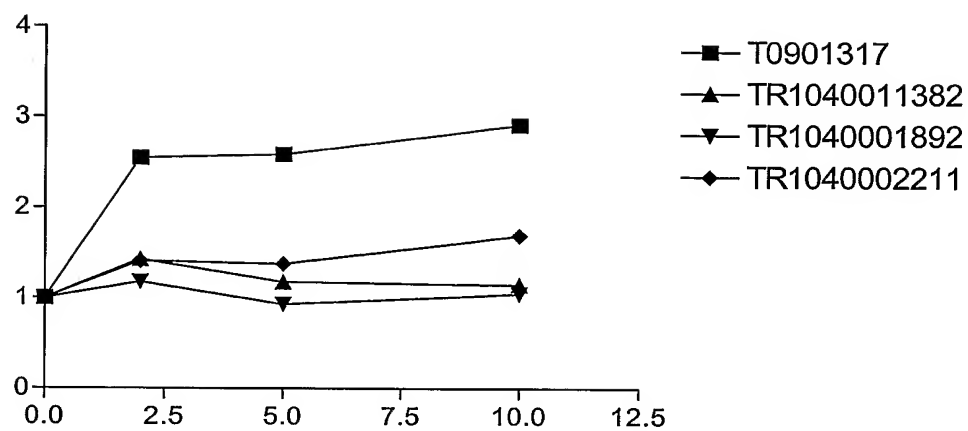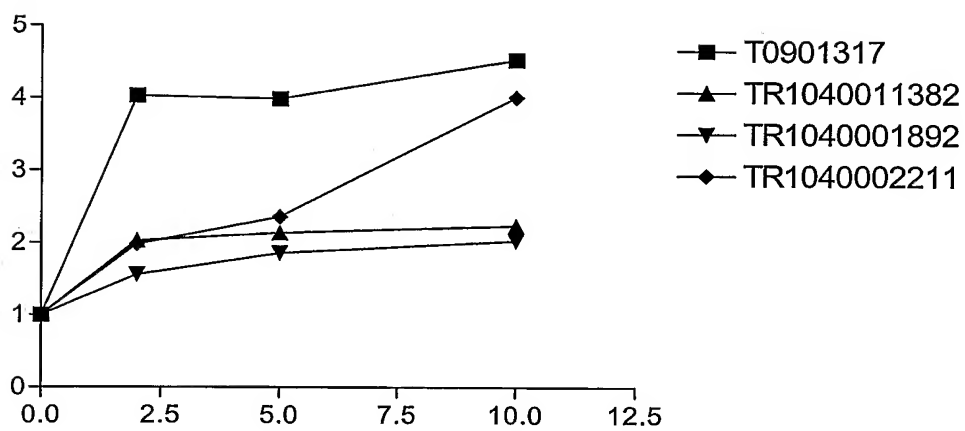
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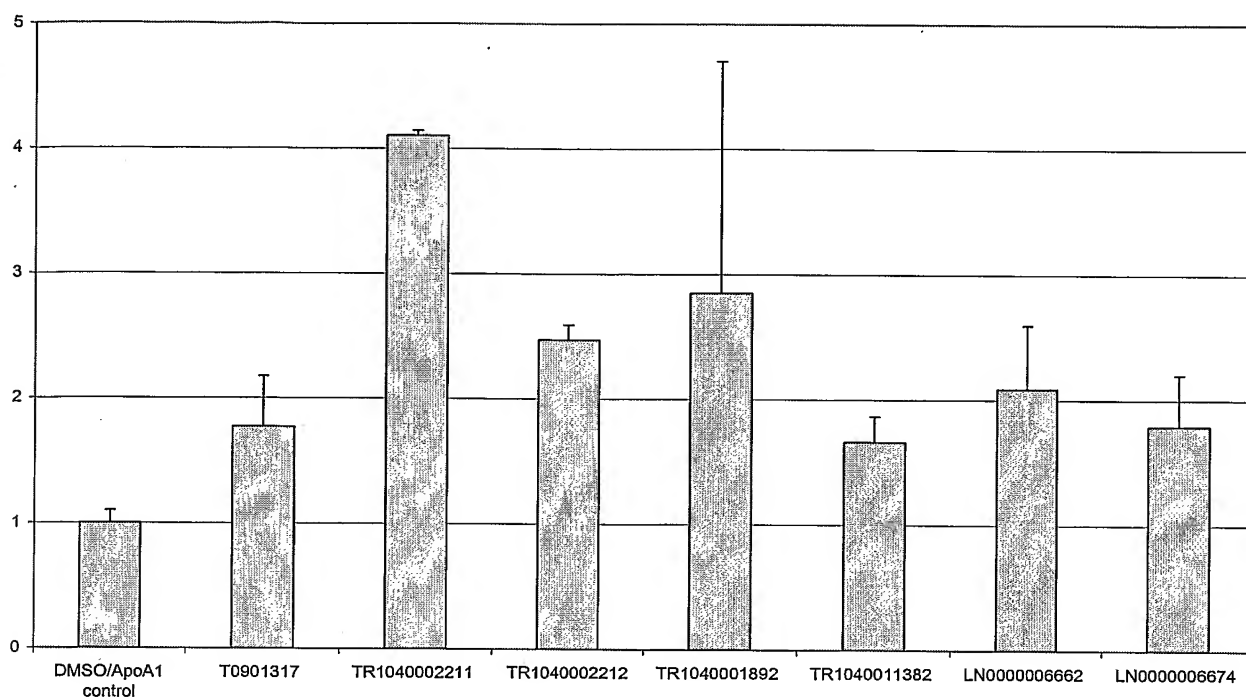
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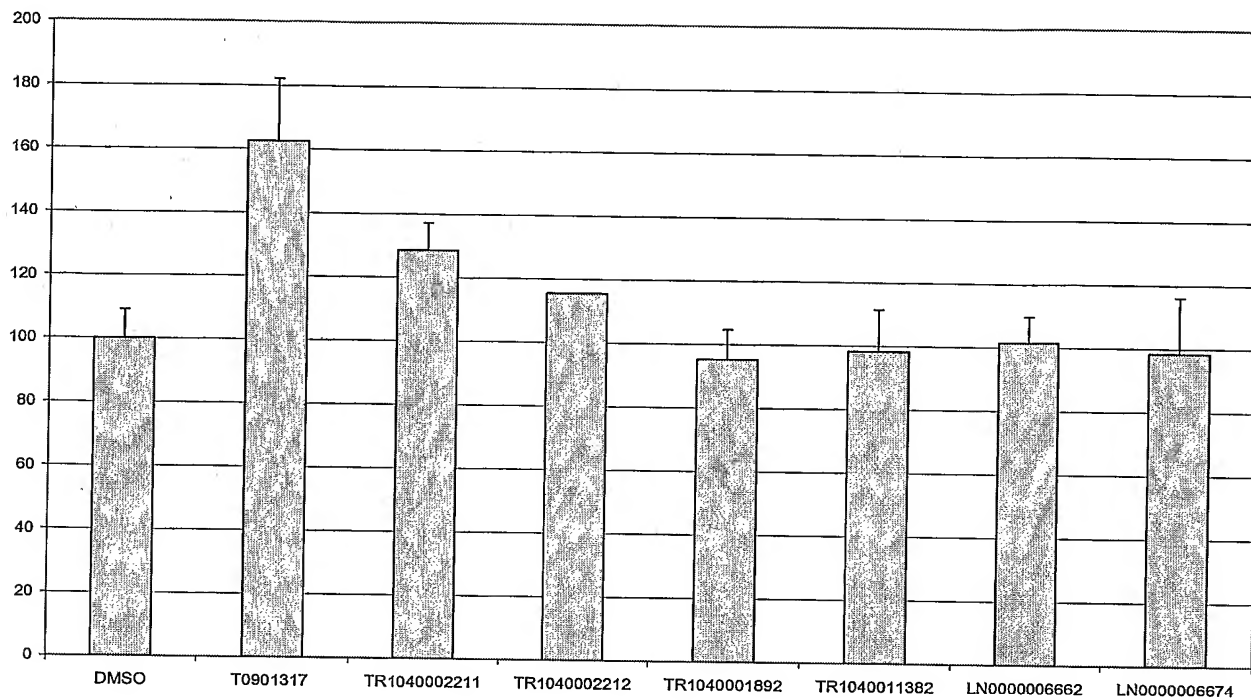
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Seite 13

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Seite 20

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<213>   Homo sapiens

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<211> 1790

<212> DNA

<213> Homo sapiens

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<211>   2688

<212>   DNA

<213>   Homo sapiens

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Seite 31

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<211> 3095

<212> DNA

<213> Homo sapiens

<400> 18
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Seite 32

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<210> 19
<211> 2128
<212> DNA
<213> Homo sapiens

<400> 19
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INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7   A61K31/517   C07D403/04   A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7   C07D   A61K   A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICES, COLUMBUS, OHIO, US; XP0002225148 ORDER NUMBER: TRG10400#07364-D; TRG10400#01815-D;TRG10400#01814-D; TRG10400#01812-D; TRG10400#01811-D; TRG10400#01809-D; TRG10400#01736-D; TRG10400#01735-D; TRG10400#01732-D;TRG10400#01729-D & "Chem.Folio" 15 May 2001 (2001-05-15), LION BIOSCIENCE , HEIDELBERG, GERMANY ————— -/--	1-3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2004	30/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Kollmannsberger, M

INTERNATIONAL SEARCH REPORT

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	COLLINS J L ET AL: "Identification of a Nonsteroidal Liver X Receptor Agonist through Parallel Array Synthesis of Tertiary Amines" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 45, 2002, pages 1963-1966, XP002225147 ISSN: 0022-2623 the whole document	1-34
A	GUPTA C M ET AL: "Drugs acting on the central nervous system. Syntheses of substituted quinazolones and quinazolines and triazepino- and triazocinoquinazolones" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 11, no. 2, 26 February 1968 (1968-02-26), pages 392-395, XP002156695 ISSN: 0022-2623 example 15; table 1	1-34
A	WO 97/20823 A (CRISCIONE LEOLUCA ; YAMAGUCHI YASUCHIKA (CH); CIBA GEIGY AG (CH); MAH) 12 June 1997 (1997-06-12) page 74; example 28 claims 1,12	1-34

INTERNATIONAL SEARCH REPORT

Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13-24, 33,34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds/compositions.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9720823	A	12-06-1997	AU	7692996 A	27-06-1997
			WO	9720823 A2	12-06-1997
			ZA	9610020 A	01-06-1997